

Radiobiological principles of fractionated radiotherapy

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The main objective of radiotherapy

To destroy all cancer cells without damaging too many normal tissue cells and thus exceeding normal tissue tolerance

Need to use the 4Rs of radiobiology to full advantage

- ◆ Repair
- ◆ Repopulation
- ◆ Reoxygenation
- ◆ Redistribution

Repair

- *Lethal damage*
- *Sublethal damage*

Lethal damage

This is damage that is irreversible and irreparable and therefore always leads to cell death

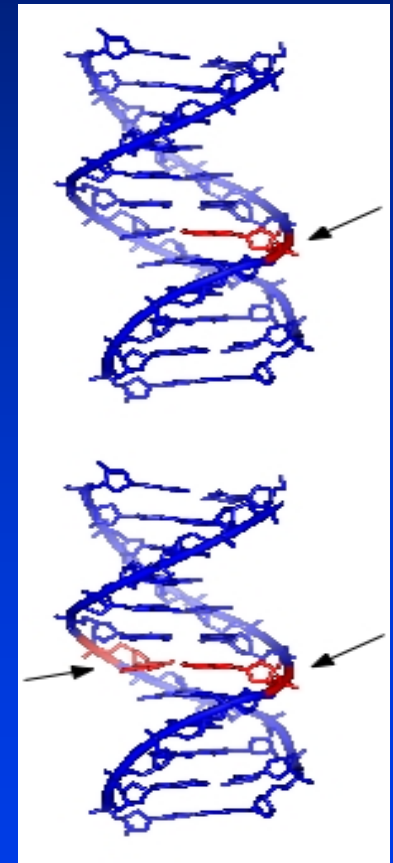
Sublethal damage (SLD)

- ◆ SLD can be repaired in hours unless additional SLD is added before repair is completed
 - *SLD repair takes time so repair increases with increase in time between fractions and decrease in dose rate*

Single strand and double strand damage

Single strand breaks (upper figure) are usually considered “repairable”

Double strand breaks (lower figure) are not usually “repairable” if the breaks are close together, since an intact 2nd strand of the DNA molecule is needed for the repair enzymes to be able to copy the genetic information



DNA repair

- ◆ DNA repair enzymes search through DNA molecules to locate damaged regions
- ◆ These enzymes may then repair the damage by a sequence much like “cut-and-paste” in computers

Repair: “cut and paste”

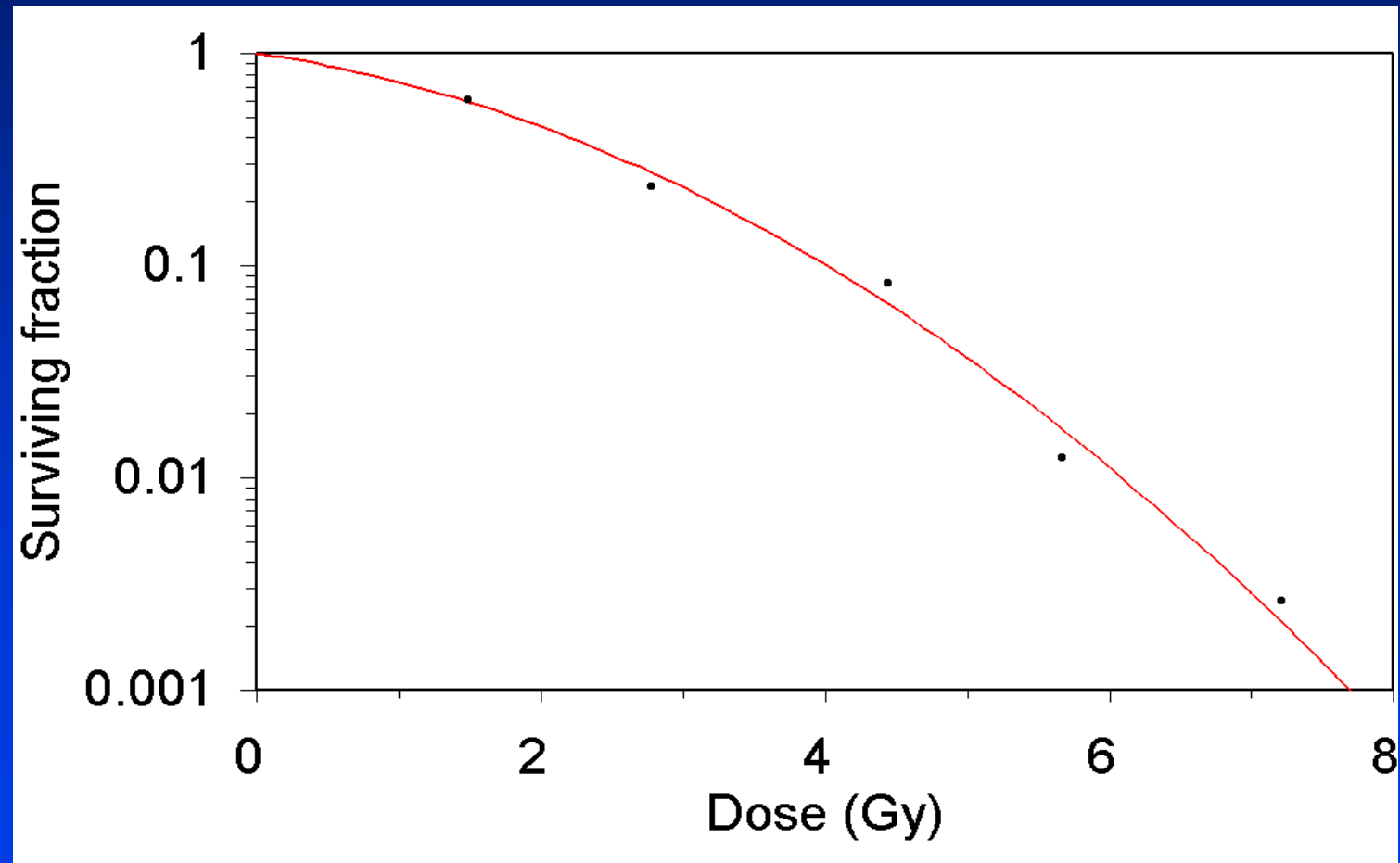
- ◆ The damaged part of one strand of the DNA molecule is “cut” and the genetic information (sequence of bases) is copied from the undamaged arm of the DNA by the repair enzyme and then “pasted” into the “gap” left in the damaged arm
 - *this “repair” takes, on average, about one hour to be completed*

The effect of dose

- ◆ At low doses (or doses/fraction), single strand breaks will dominate i.e. repair is common
- ◆ At high doses, double strand breaks will be common i.e. little repair
 - *consequently survival curves get steeper as dose increases*

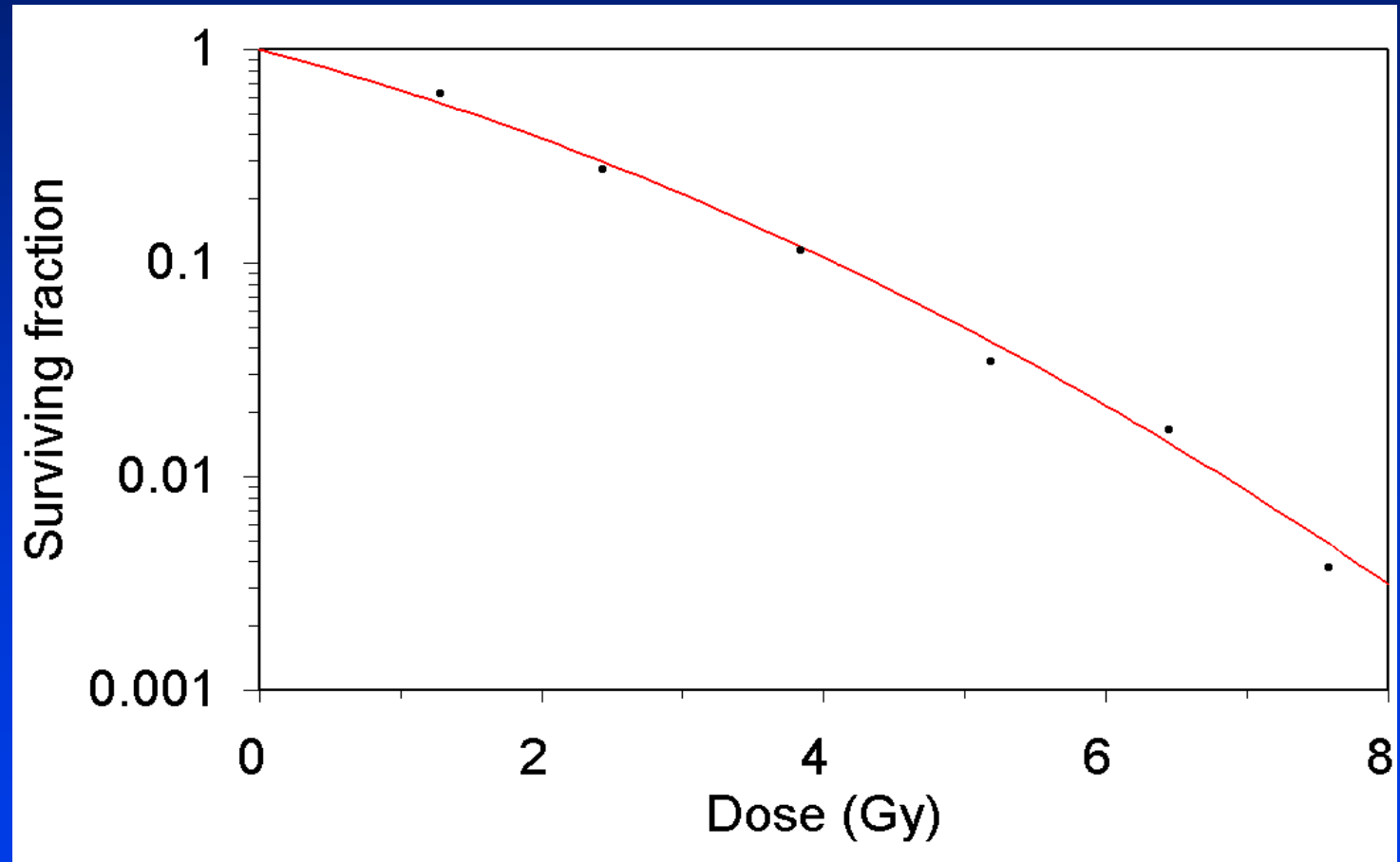
As dose increases survival curves become steeper

The more repair the curvier the survival curve



Survival curve for cells that exhibit little repair

Note that the survival curve remains much straighter



SLD repair: the effect of fractionation

- ◆ SLD repair (and hence surviving fraction) will increase as fractionation increases i.e. lower doses/fraction
- ◆ Full repair of SLD will occur if enough time is allowed between fractions
- ◆ Daily fractionation is usually considered quite adequate for full repair of SLD

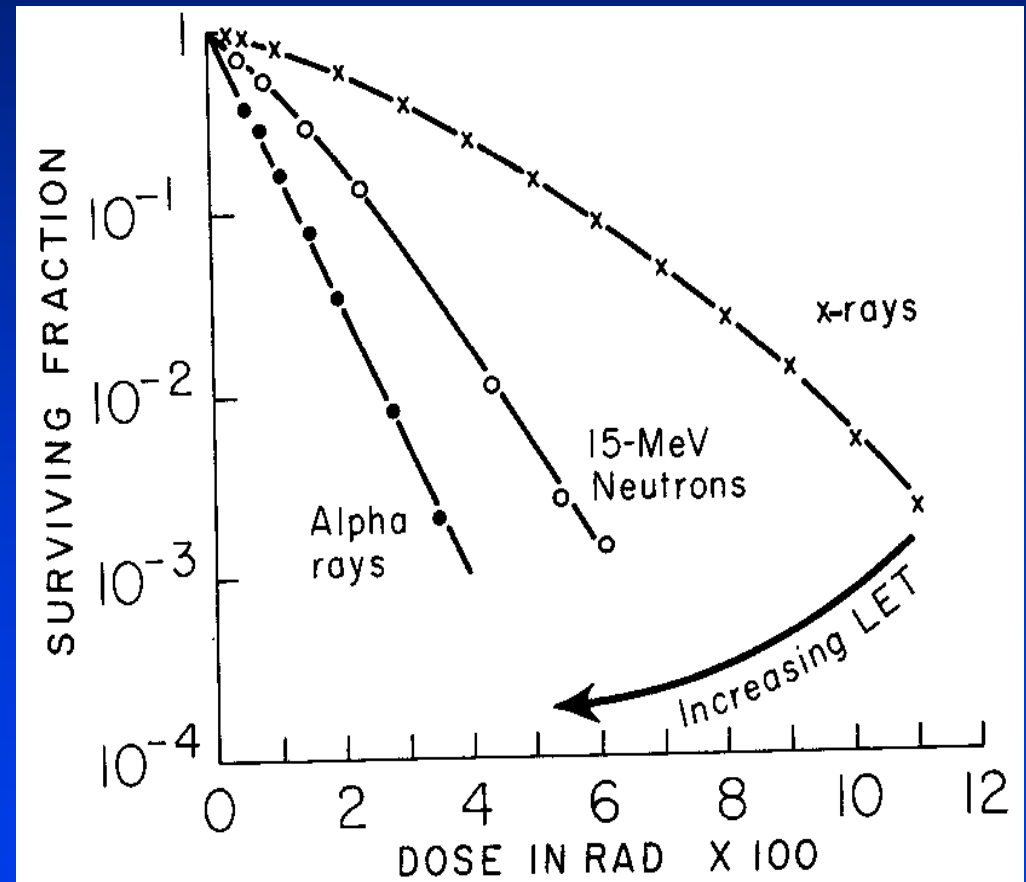
Effect of LET on cell survival curves

As LET increases, double strand breaks are common and the curves become more linear and steeper

The increase in sensitivity is represented by the RBE

$$RBE = \frac{\text{dose of } ^{60}\text{Co radiation}}{\text{dose of different LET radiation}}$$

to produce the same biological effect



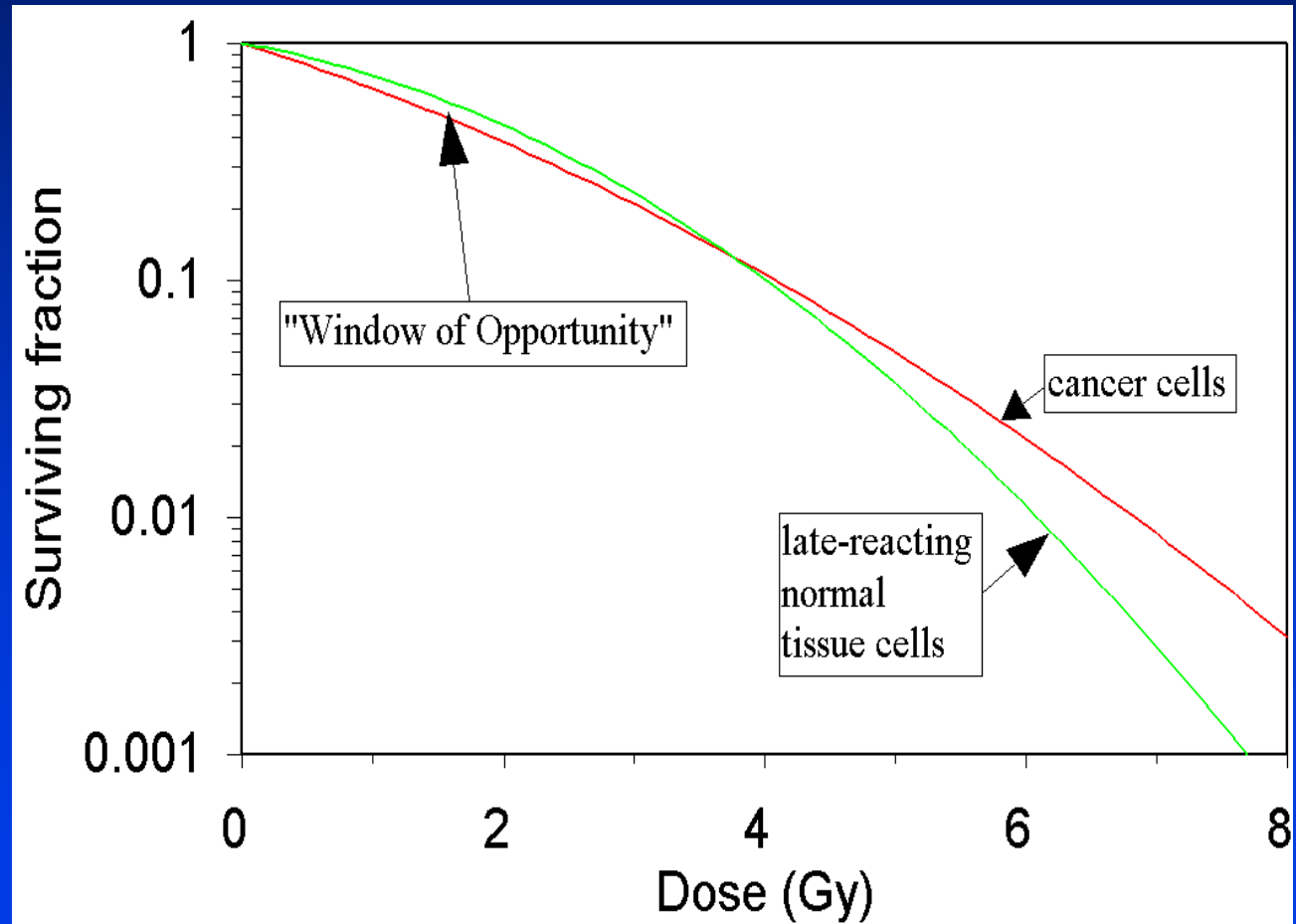
Survival curves: normal vs cancer cells

- ◆ Cancer cells do not “repair” damage at low doses as well as do normal tissue cells
 - *there is a “window of opportunity” at low doses where the survival of late-reacting normal tissue cells exceeds that of cancer cells*

Cell survival curve comparison: the “Window of Opportunity”

At low doses, the survival of normal tissue cells (green curve) exceeds that of cancer cells

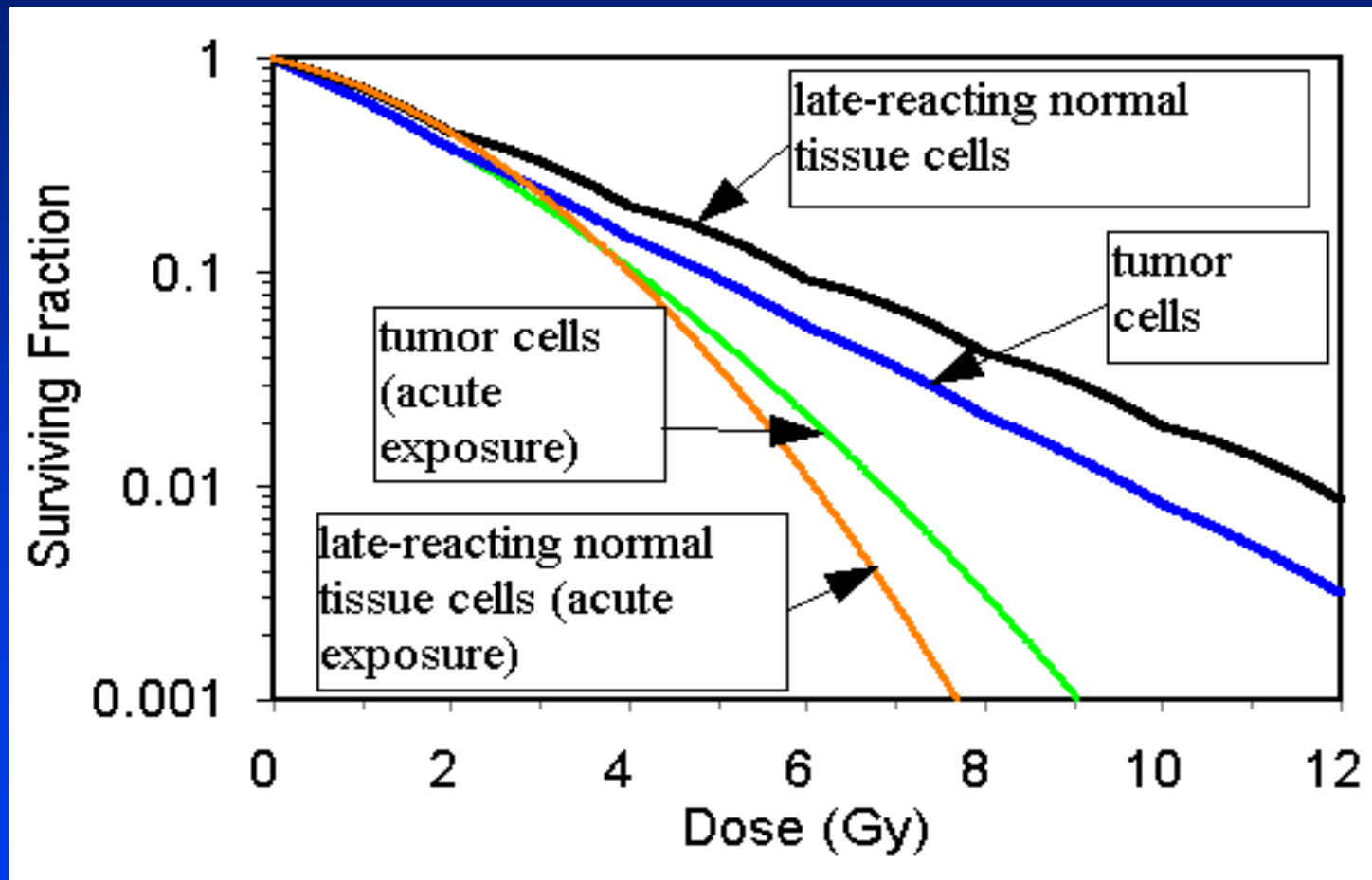
At high doses, the survival of cancer cells (red curve) exceeds that of normal tissues



Fractionation

- ◆ This is why we typically fractionate radiotherapy at low doses/fraction
- ◆ We need to fractionate at doses/fraction within this “window of opportunity” e.g. typically about 2 Gy/fraction

Normal vs cancer cells for fractionation at 2 Gy/fraction



Cell survival curve comparison: the “Window of Opportunity”

Note that we have assumed that the dose to normal tissues is the same as the dose to the cancer cells, but is this a reasonable assumption if we are using conformal teletherapy or brachytherapy?

Is this a reasonable assumption?

- ◆ No, because the major advantage of conformal radiotherapy is that the dose to normal tissues is kept less than the tumor dose
- ◆ Hence the *effective dose** to normal tissues will usually be less than the *effective dose* to tumor

* *the effective dose is the dose which, if delivered uniformly to the organ or tumor, will give the same complication or cure rate as the actual inhomogeneous dose distribution*

Geometrical sparing factor

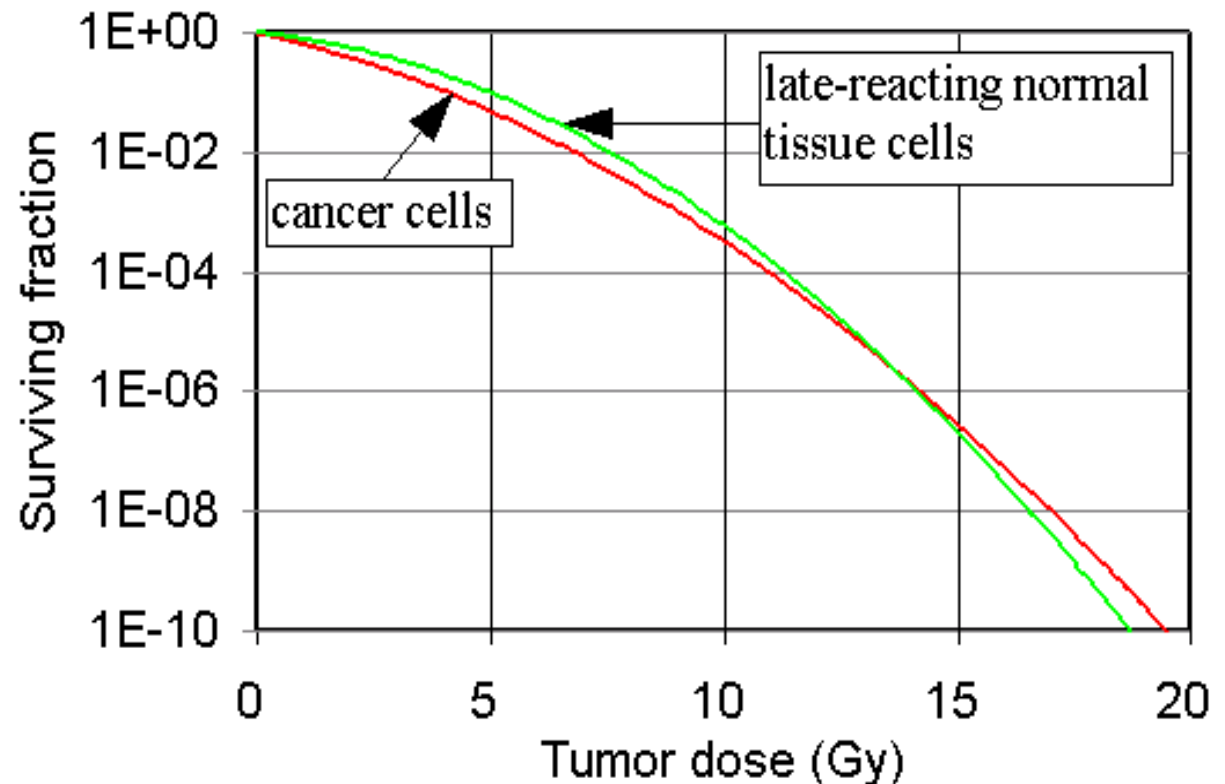
We can define a “geometrical sparing factor”, f , such that:

$$f = \frac{\text{effective dose to normal tissues}}{\text{effective dose to tumor}}$$

The “window of opportunity” widens with geometrical sparing

Even with a modest geometrical sparing of only 20%, the “window of opportunity” extends to over 10 Gy

Effect of geometrical sparing, $f = 0.8$



This means that:

We can safely use much higher doses per fraction

- *for teletherapy i.e. hypofractionation*
- *for brachytherapy i.e. HDR*

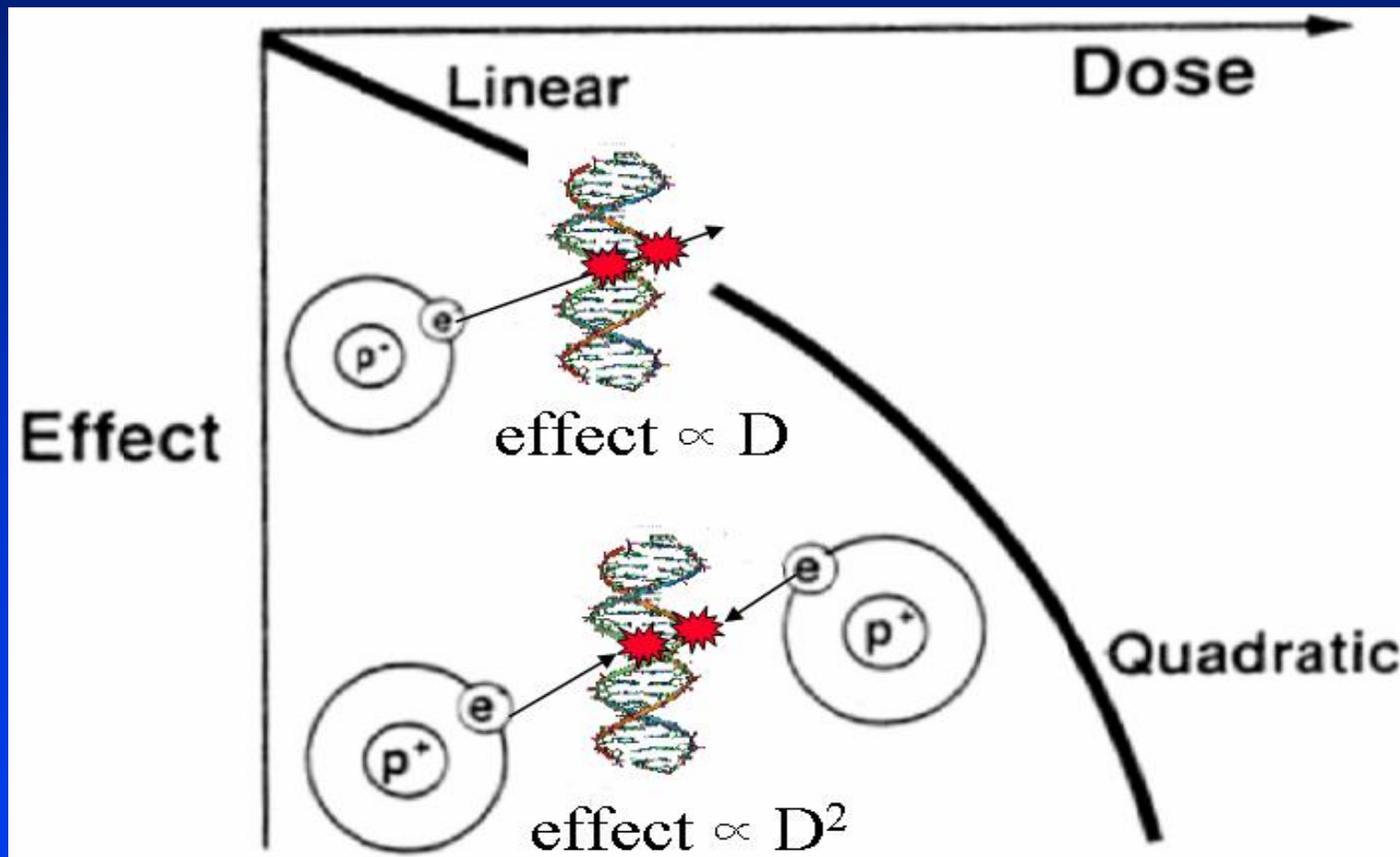
How can we determine the “best” fractionation to use?

- ◆ We need a mathematical model that describes the effects of radiotherapy on cancer and normal tissue cells
 - *this is the linear-quadratic model*

The linear-quadratic model of cell survival: two components

- ◆ Linear component:
 - a double-strand break caused by the passage of a single charged particle e.g. electron, proton, heavy ion
- ◆ Quadratic component:
 - two separate single-strand breaks caused by different charged particles

The linear-quadratic model



Linear component: Poisson statistics

Statistics of rare events: for cells exposed to the passage of a single charged particle, the probability that any given target within the cell will suffer a lethal event will be very low.

The probability of x lethal events/cell, $P(x)$, where the mean number of events/cell = m , is given by:

$$P(x) = \frac{e^{-m} m^x}{x!}$$

Poisson Statistics: cell survival

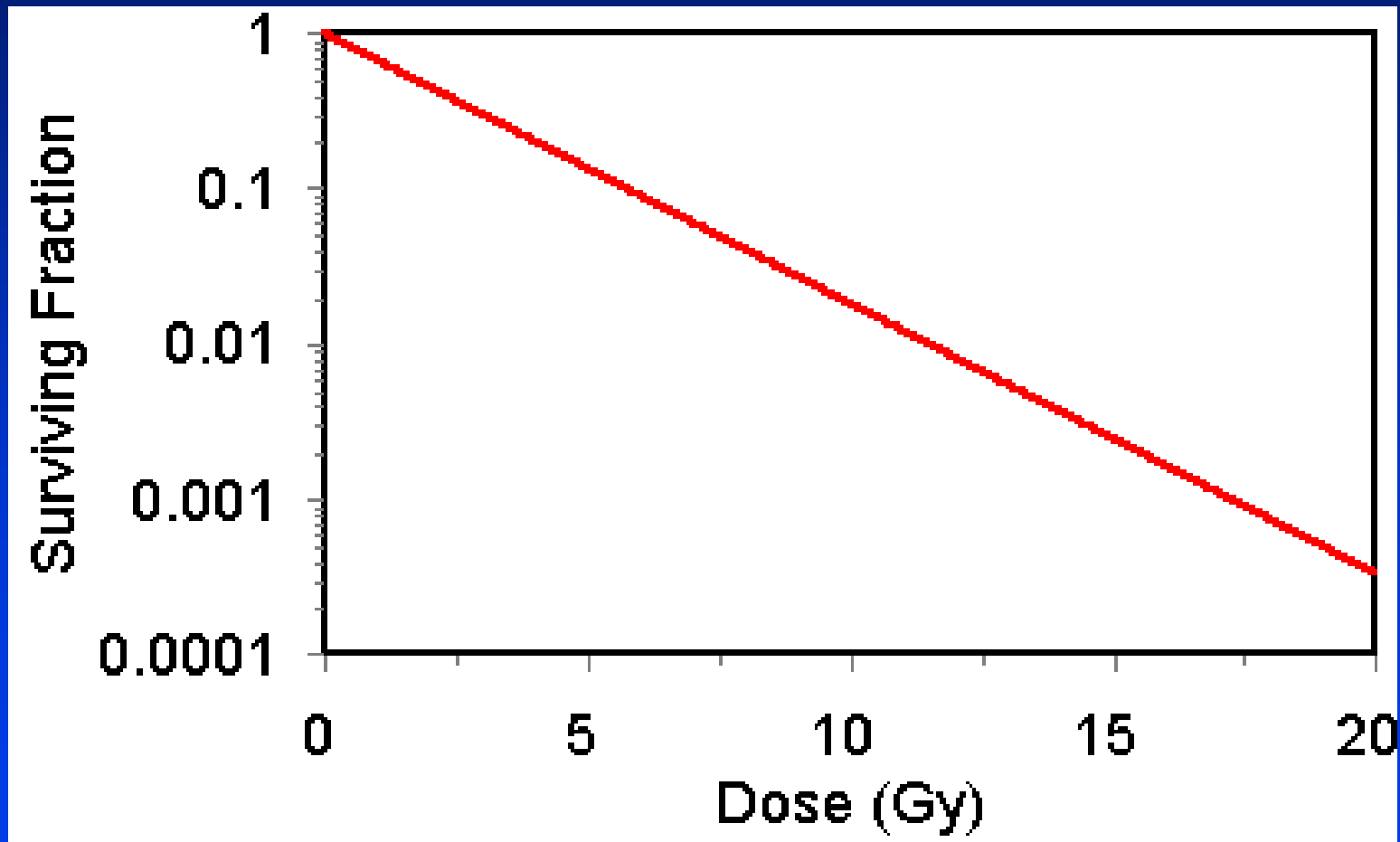
Cell-surviving fraction, S , the probability of no lethal events/cell (i.e. $x = 0$), is therefore given by:

$$S = P(0) = \frac{e^{-m} m^0}{0!} = e^{-m}$$

But m is a linear function of dose, D , i.e. $m = \alpha D$.

Hence:
$$S = e^{-\alpha D}$$

Linear component: $\ln S = -\alpha D$



The quadratic component: β -type damage

- ◆ The probability that one DNA strand break will occur is linearly proportional to dose, D
- ◆ The probability that an adjacent part of the other DNA strand will be hit in an independent event is also proportional to dose, D
- ◆ Probability that both events will occur is, therefore, proportional to D^2
- ◆ Hence: $S = e^{-\beta D^2}$

The L-Q Model Equation

$$\ln S = -(\alpha D + \beta D^2)$$

α represents the probability of lethal α -type damage

β represents the probability that independent β -type events have combined to produce lethal events e.g. double-strand breaks

Problem with the L-Q model

- ◆ There are too many unknown biological parameters in the basic L-Q equation (α and β) for reliable values to be determined from analysis of clinical data
- ◆ These can be reduced to one parameter by dividing $-\ln S$ by α

The BED equation for fractionated radiotherapy in N fractions each of dose d

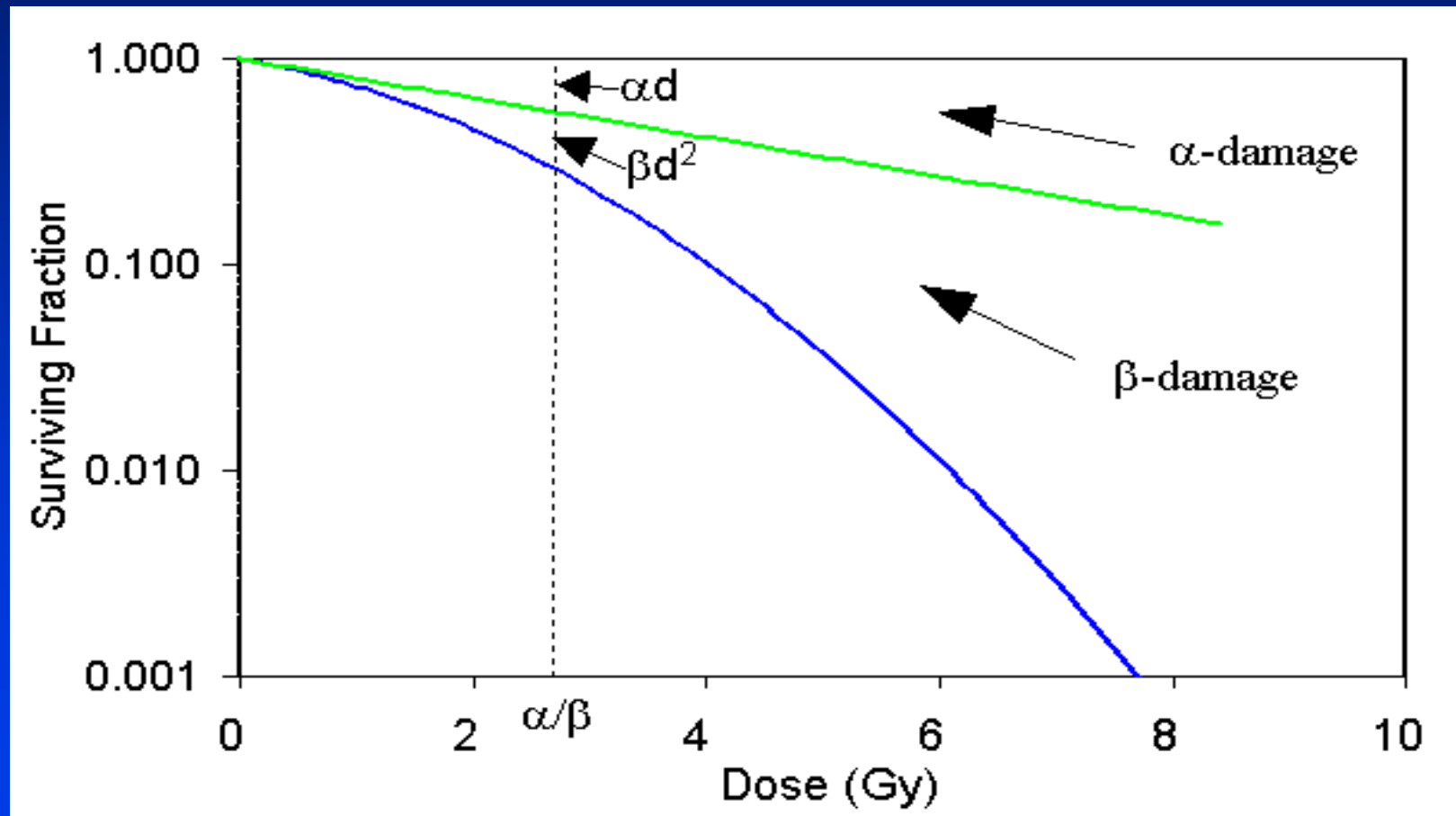
$$- \ln S = N(\alpha d + \beta d^2)$$

Hence:

$$BED = \frac{-\ln S}{\alpha} = Nd \left(1 + \frac{d}{\alpha / \beta} \right)$$

The remaining unknown biological parameter is α/β

The L-Q Model: α/β is the dose where α -damage equals β -damage



Typical values for α/β

The most common assumptions are:

for tumors and acute reactions:

$$\alpha/\beta = 10 \text{ Gy}$$

for late-reacting normal tissues:

$$\alpha/\beta = 2 - 3 \text{ Gy}$$

*

Note that some recent studies have reported that the α/β value for prostate cancer may be as low as 1.5 Gy and for breast cancer as low as 4 Gy

Repopulation

During a course of radiotherapy cells that have been killed are replaced by new cells generated by division of those that have survived

How important is repopulation?

Tumors

- *very important, especially for rapidly growing cancers*

Normal tissues

- *negligible for late-reacting tissues*
- *important for acutely-reacting tissues, especially for short courses of treatment*

Repopulation

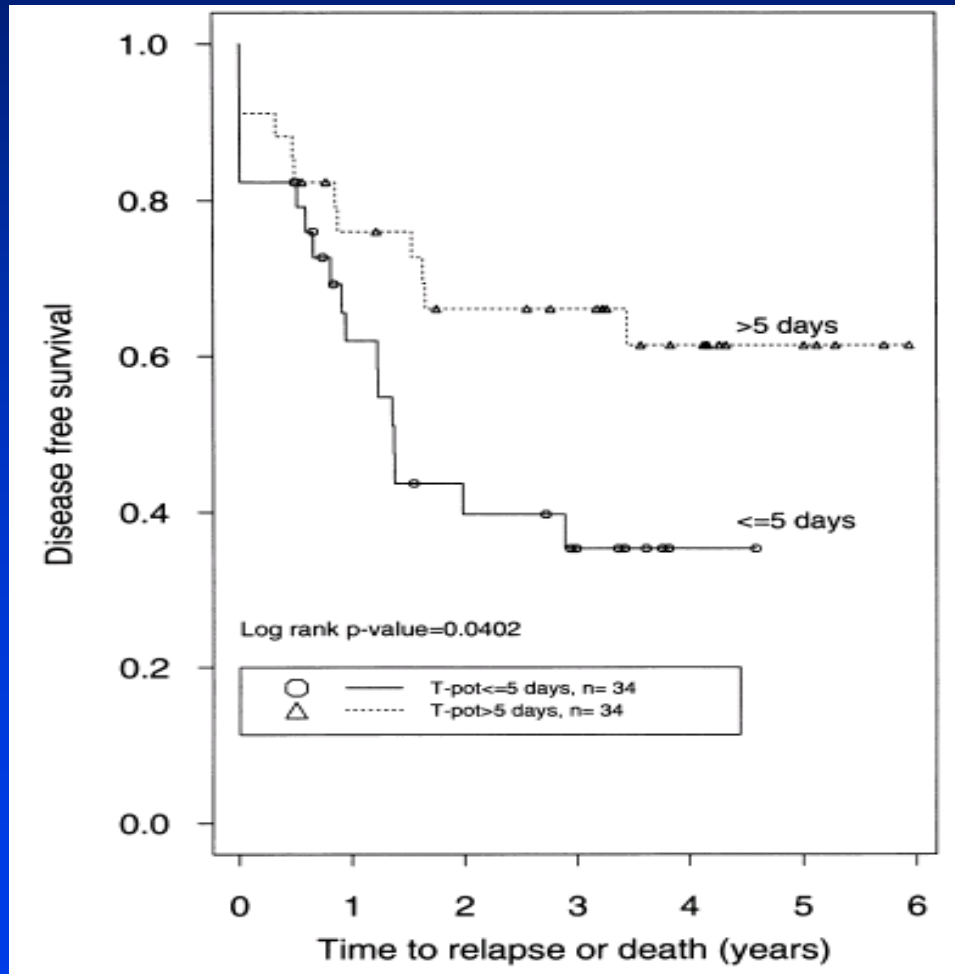
Usually represented by T_{pot}
which is the doubling time of
the cells capable of continued
proliferation

Effect of T_{pot} on outcome

Tumor cells with short T_{pot} need to be treated with accelerated therapy otherwise they will repopulate faster than they can be treated

T_{pot} and survival for cervix cancer patients treated with radiation

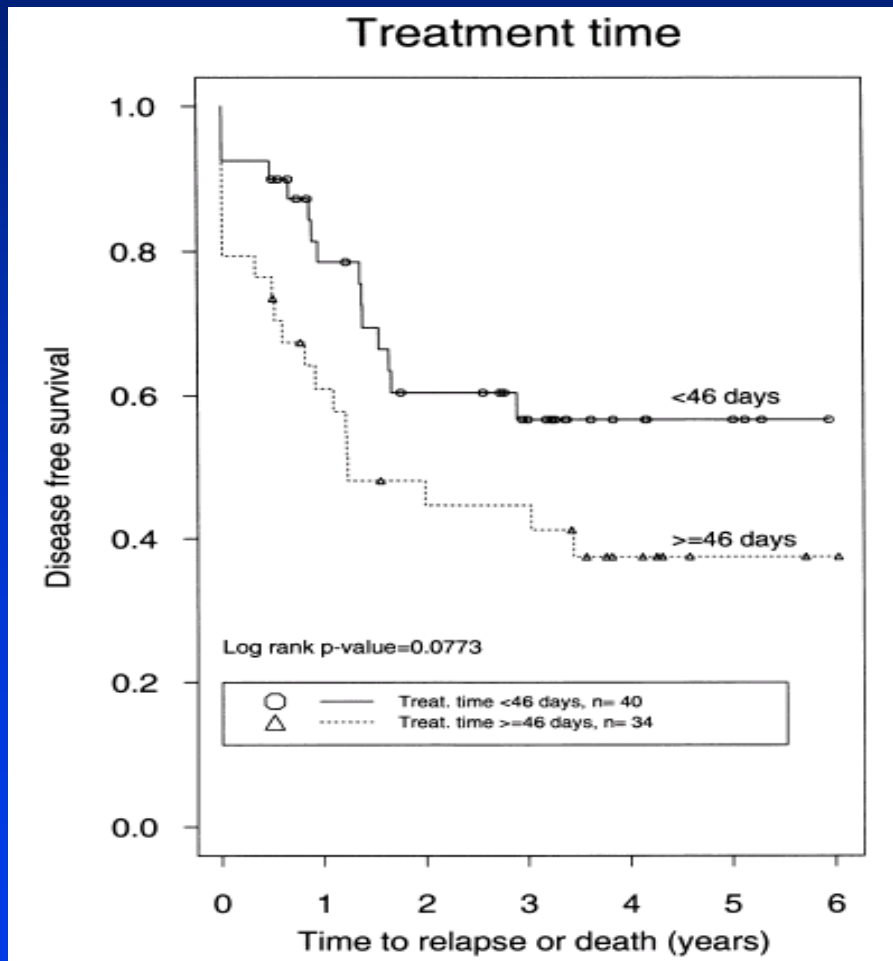
Tsang, et al., Radiother. And Oncol. 50: 93-101, 1999.



Patients in whom the cancer cells have a long T_{pot} (> 5 days) have a greater probability of survival than those in whom the T_{pot} is short

Overall treatment time and survival for cervix cancer patients treated with radiation

Tsang, et al., Radiother. And Oncol. 50: 93-101, 1999.



Because some of the cancer cells in some of the patients reproduce rapidly (i.e. have a short T_{pot}), some of the patients who are treated over a longer time (i.e. >46 days) will be less likely to survive

It is assumed that repopulation increases cell survival exponentially with time

$$-\ln S = N(\alpha d + \beta d^2) - \frac{0.693T}{T_{pot}}$$

where T is the overall treatment time and T_{pot} is the doubling time of the cells capable of continued proliferation

BED equation with repopulation

$$BED = Nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{0.693T}{aT_{pot}}$$

where the tissue-specific radiobiological parameters are α/β , α , and T_{pot}

Problem with the BED equation with repopulation

- ◆ As before, there are too many unknown biological parameters in this L-Q equation (α , α/β and T_{pot}) for reliable values to be determined from analysis of clinical data
- ◆ These can be reduced to two parameters by replacing $0.693/\alpha T_{pot}$ by k

The BED equation with repopulation

$$BED = Nd \left(1 + \frac{d}{\alpha / \beta} \right) - kT$$

The remaining unknown biological parameters are α/β and k

Typical values for k assumed for normal tissues

Acutely responding normal tissues:

- *0.2 - 0.3/day*

◆ Late responding normal tissues:

- *0 - 0.1/day*

Typical values for k assumed for tumors

Growth rate of tumor	k (day ⁻¹)
slow	about 0.1
average	about 0.3
rapid	about 0.6

Reoxygenation: The Oxygen Effect

- ◆ Oxygen is a powerful radiation sensitizer
- ◆ The blood (and hence O₂) supply to some cancer cells is often reduced as the tumor grows
 - *these cells will be more resistant to radiation*

The Oxygen Enhancement Ratio

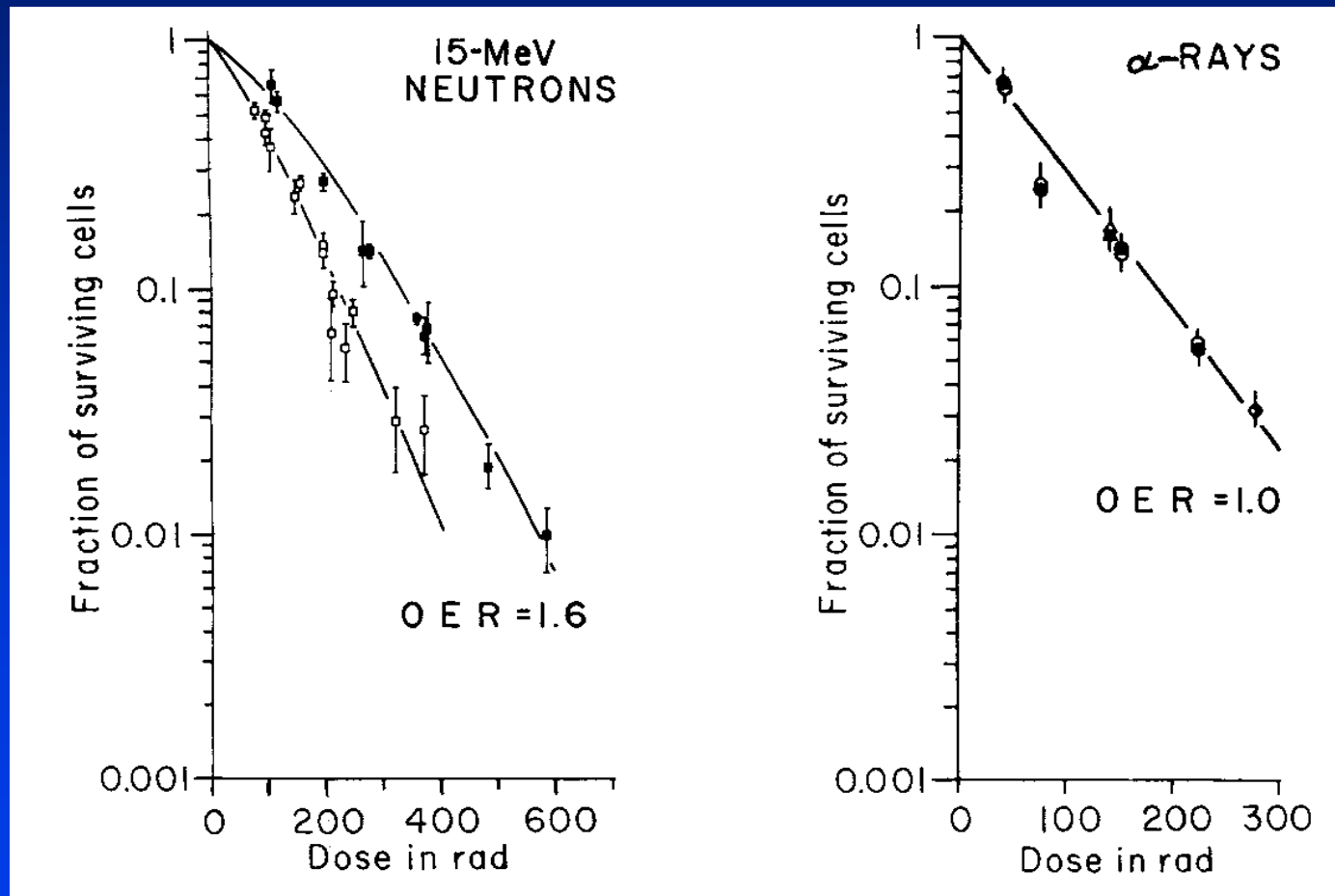
- ◆ The degree of sensitization is expressed in terms of the Oxygen Enhancement Ratio, where:

$$OER = \frac{\text{dose under hypoxic conditions}}{\text{dose under aerobic conditions}}$$

to produce the same biological effect

- ◆ OERs with x rays are typically about 3

OER decreases as LET increases



Evidence for the effect of hypoxic cells in human tumors

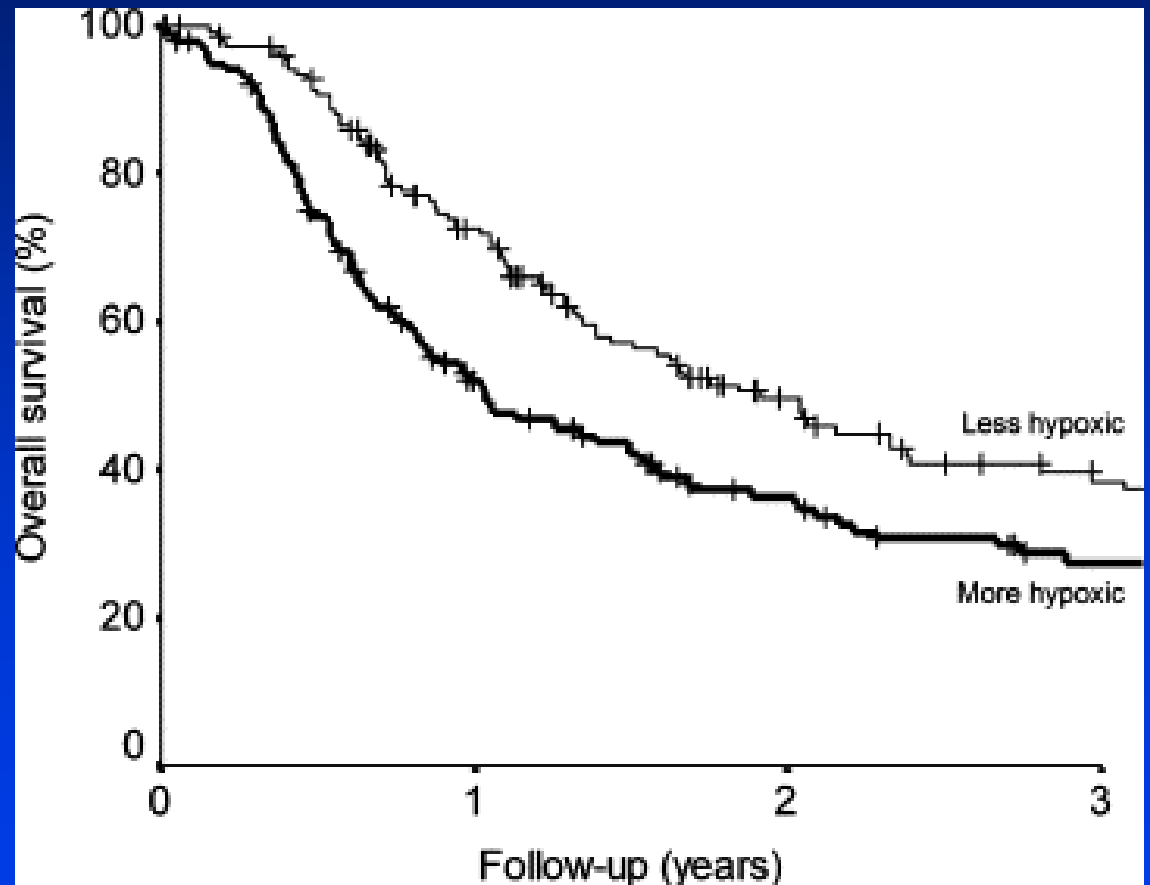
Oxygen probe measurements and pretreatment hemoglobin levels

- *low O_2 and low hemoglobin levels correlate with poor local control*

Effect of tumor oxygenation in head & neck cancers

Nordsmark, et al. Radiother. & Oncol. 77, 18-24 (2005)

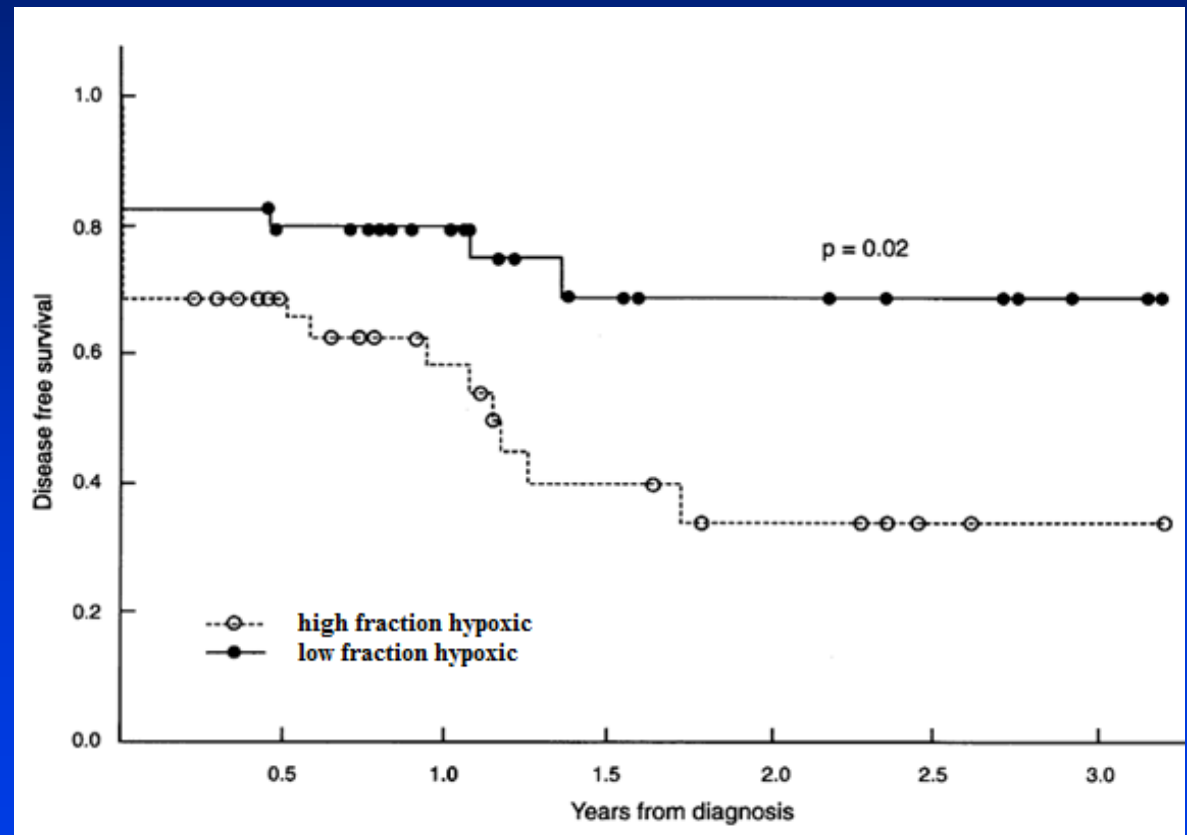
Actuarial overall survival rate for patients with less hypoxic tumors (thin line) compared with more hypoxic tumors (thick line), $P=0.006$.



O₂ probe measurements and survival of cervix cancer patients treated with radiotherapy

Note that immediately after diagnosis the survival of patients with hypoxic cancers is lower

Apparently hypoxic cancers are more aggressive as well as more resistant to radiotherapy

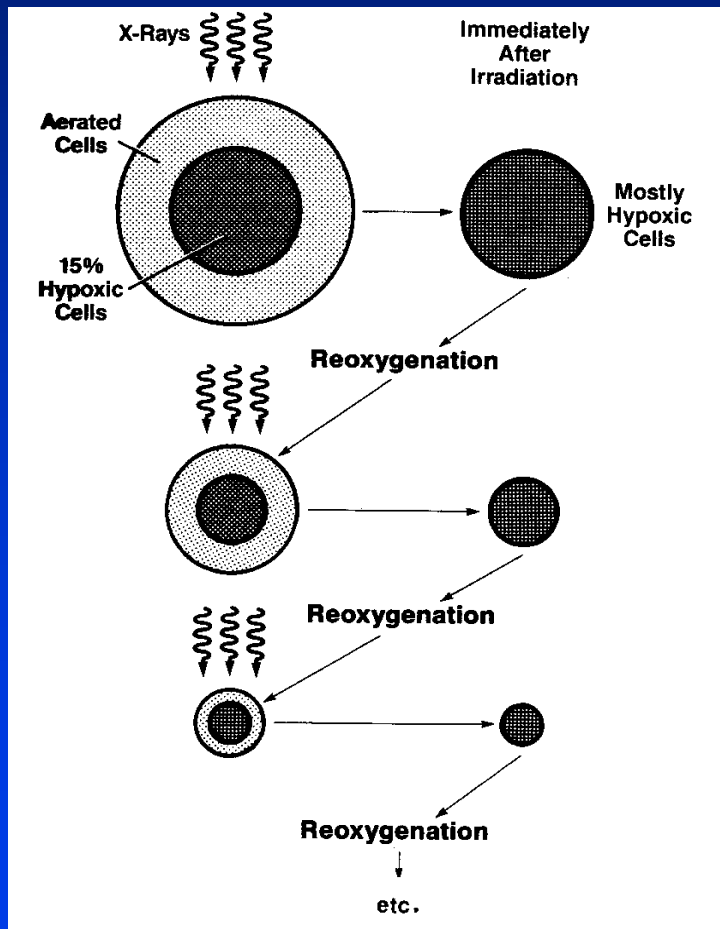


Fyles, et al. *Radiotherapy and Oncology* 48 (1998) 149–156

Reoxygenation

- ◆ As the tumor shrinks, cells previously beyond the range of oxygen diffusion find themselves closer to blood vessels and reoxygenate
- ◆ Revascularization of the tumor and killing of well-oxygenated cells might also increase the availability of oxygen

The process of reoxygenation during fractionated radiotherapy



After each fraction, most of the surviving cells are hypoxic since these are the most resistant cells

Between fractions, these cells tend to reoxygenate prior to delivery of the next fraction

Importance of reoxygenation in radiotherapy

- ◆ Spreading irradiation over long periods of time by fractionation or very low dose rate brachytherapy (e.g. permanent implants) ought to be beneficial if some of the cells are hypoxic
 - *but beware of rapidly growing cancers*

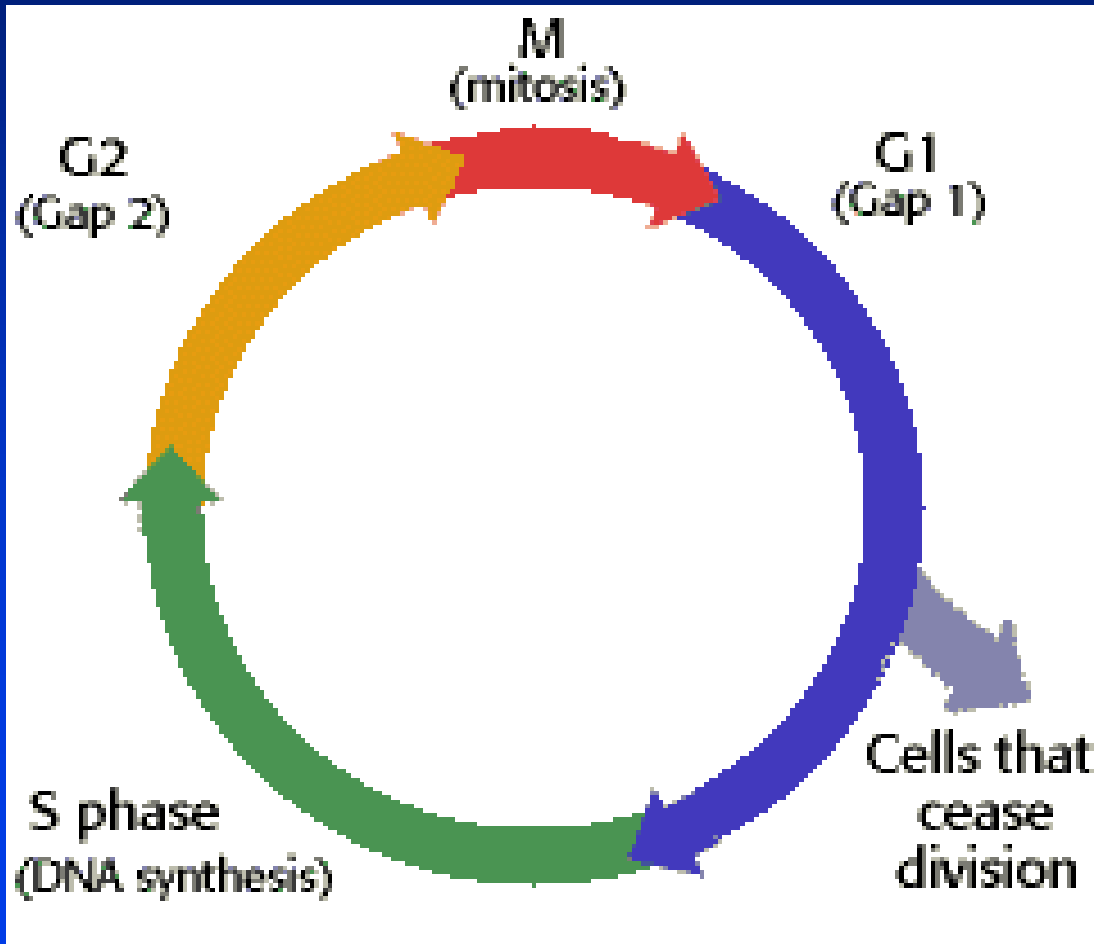
Redistribution: the cell cycle effect

- ◆ Cells are most sensitive at or close to mitosis
- ◆ Resistance is usually greatest in the latter part of the S phase

Potential influence of the cell cycle effect in radiotherapy

- ◆ Cancer cells and cells of acutely responding normal tissues are often in mitosis and hence will be most sensitive to radiation
- ◆ Cells of late reacting normal tissues are rarely in mitosis and hence will be relatively resistant
- ◆ Some cancer cells may be “trapped” in resistant phases of the cell cycle and thus be difficult to kill

The cell cycle



Late reacting normal tissue cells that are not rapidly dividing or have ceased division, and possibly some cancer cells, might be “trapped” in a resistant part of the G_1 phase

Cell-cycle times

- ◆ Typically, cell cycle times vary from as little as 10 hours up to several hundreds of hours
- ◆ The major reason for the variation in cell-cycle times is the highly-variable length of G_1

Variation of cell survival curve shape during the cell cycle

- ◆ Survival curves for cells in the M phase are linear, indicating the absence of any repair
 - *this is why the cell survival curves for cancer cells (which are often in mitosis) are more linear (higher α/β) than those for cells of late-reacting normal tissues*

Redistribution

- ◆ Because of the cell cycle effect, immediately after a radiation exposure the majority of cells surviving will be those that were in a resistant phase of the cell cycle at the time of irradiation, such as late-S or maybe in a resistant part of the G_1 phase
- ◆ After exposure, cells are thus partially synchronized
- ◆ This is known as *redistribution* (or *reassortment*)

Redistribution

- ◆ The timing of the subsequent fraction will, therefore, make a difference in the response.
- ◆ For example, if the next fraction is delivered at a time when the synchronized bolus of cells has reached a sensitive phase of the cell cycle, then the cells will be extra sensitive.

Redistribution

- ◆ Clearly, this depends on both the length of the various phases of the cell cycle and the time between fractions.
- ◆ Since 24 hours is much longer than the length of the G_2 phase of the cell cycle for most cells, it is likely that such sensitization will be unlikely to play a significant role for treatments delivered with daily fractionation.

Redistribution

- ◆ However, with twice or three-times-a-day fractionation, sensitization by the redistribution effect is conceivable and could be significant.
- ◆ This might be one of the reasons why some clinical trials of hyperfractionation, accelerated hyperfractionation, or dynamic fractionation have been successful or have failed.

Different fractionation schemes

- ◆ Many different fractionation schemes have been devised to address certain situations such as when:
 - *normal tissue tolerance will be exceeded with conventional fractionation*
 - *there is considerable “geometrical sparing” of normal tissues*
 - *cancers are proliferating too fast*
 - *cancer cells are “trapped” in a resistant phase of the cell cycle or are resistant due to hypoxia*

Fractionation schemes:

I. Conventional fractionation

- ◆ Dose/fraction: 1.8 - 2.2 Gy
- ◆ Fractions/week: 5
- ◆ Total dose: 50 - 80 Gy
- ◆ Used for most patients

Conventional fractionation: potential problems

- ◆ May be too slow for the treatment of fast-growing cancers
- ◆ Total dose may be too low for some resistant cancers

II. Hyperfractionation

- ◆ Dose/fraction: 1.1 - 1.3 Gy
- ◆ Fractions/week: 10
- ◆ Total dose: 60 - 70 Gy
- ◆ Used when late normal tissue tolerance is a major problem (low dose/fraction means more repair)

Hyperfractionation: potential problems

- ◆ The relatively short time between the fractions each day might not be sufficient for complete repair
 - *this is likely to be a disadvantage for normal tissue cells since they tend to repair better than cancer cells if given sufficient time*
 - *must allow at least 6 hours between fractions*

III. Accelerated fractionation

- ◆ Dose/fraction: 1.4 (with 2 fractions/day)
- 2.5 Gy (with 1 fraction/day)
- ◆ Fractions/week: 5 - 10
- ◆ Total dose: 40 - 50 Gy
- ◆ Used for rapidly growing cancers

Accelerated fractionation: potential problems

- ◆ Early responding normal tissues may not have time to repopulate in the 3 - 4 week course, so acute reactions are of major concern
- ◆ Must allow at least 6 hours between fractions


IV. Hyperfractionated accelerated fractionation

- ◆ Dose/fraction: 1.5 Gy
- ◆ Fractions/week: 15 – 21
 - *if delivered without weekend breaks (i.e. 21 fractions/week) called Continuous Hyperfractionated Accelerated Radiation Therapy (CHART)*
- ◆ Total dose: 54 Gy
- ◆ Used for very rapidly growing cancers

Hyperfractionated accelerated fractionation: potential problems

- ◆ Acute reactions can be excessive
- ◆ The relatively short time between the fractions each day might put normal tissues at extra risk of damage because cells will not have time for complete repair
 - *must allow at least 6 hours between fractions*

Hypofractionation

- ◆ Dose/fraction:  2.4 Gy
- ◆ Fractions/week: 1 - 5
- ◆ Total dose: 10 - 60 Gy
- ◆ Used for palliation or when there is considerable geometrical sparing of normal tissues

Hypofractionation: potential problems

- ◆ Because of the risk of late complications, the total dose must be considerably less than that needed to cure cancers, so this is usually for palliation only
 - *however, if the dose to normal tissues could be kept low, as with highly conformal therapy (IMRT, etc.), it might be possible to use hypofractionation for curative patients*

Radiobiological principles of fractionated radiotherapy: Summary

- ◆ Cells of late-reacting normal tissues tend to repair better than cancer cells
- ◆ The L-Q model can be used to represent cell survival
- ◆ Using the 4Rs of radiobiology we ought to be able to optimize fractionation